REMARKS

The Office Action is indicated as non-final. Further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, is respectfully requested.

The Office Action Summary correctly indicates that claims 52-101 are pending in the application. Claims 52-101 are subject to a restriction requirement. Claims 53-58, 62, 64-68, 92-94 and 96-101 have been withdrawn from consideration. Claims 52, 59-61, 63, 69-91 and 95 are under consideration and stand rejected.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 52-59-61, 63, 69-91 and 95 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to enable a person of skill in the art to make and/or use the claimed invention. The alleged basis of the rejection is as set forth in the Office Action mailed February 10, 2004 and restated in the Office Action mailed October 8, 2004. Applicants respectfully traverse the rejection.

Taken together with all the evidence, each item given as much weight as is due, the documents cited by the Office fail to provide a basis to support the asserted rejection. The Office bases the rejection on the allegation, which has been proven false, that "Whereas tolerance has been repeatedly induced in mice, the identical/equivalent methods have not worked in humans." Office Action mailed 10/08/2004 at 2. Even if the allegation were true, the Federal Circuit has recognized that "[t]he mere fact that something has not previously been done clearly is not [] a sufficient basis for rejecting all applications purporting to disclose how to do it." *Gould v. Quigg*, 3 U.S.P.Q. 2d 1302, 1304 (Fed. Cir. 1987).

Applicants have submitted direct *in vivo* evidence of the enablement of the method in an art accepted animal model. Mice are an art accepted model in this field, as evidenced by the widespread use of mouse models in studying immunological phenomena, which are both directly reported and referenced in the publications that have been made of record. The Federal Circuit has stressed that precedential authority "has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995).

The Office has relied upon a trade paper report of the cessation of a clinical trial as evidence of non-enablement. Office Action mailed 2/10/2004 at 3 (*citing Marketletter* (1999)). However, the cited article reports upon cessation of a clinical trial that used a distinct method. This decision depended on FDA regulatory and economic factors which do not bear on the enablement of the presently claimed methods. The Patent Office is not the FDA. FDA approval is not required to demonstrate utility or enablement of a method with therapeutic uses. Such a standard would render it basically impossible for those working in the pharmaceutical industry to ever obtain valid patents. The Federal Circuit has recognized this inequity, and has cautioned the PTO not to "confuse[] the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. *In re Brana* at 1442-43. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. *Id.*

The fact of the phenomena that underlies and enables the claimed methods is never denied in any publication cited by the Office. At most, the documents cited by the Office demonstrate the results of experimentation into the effectiveness of particular varying treatment parameters. Even if experimentation to optimize treatment parameters may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See, e.g., In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976); M.P.E.P. § 2164.01.

Applicants have provided more than sufficient documentary and testimonial evidence that refutes the allegations of the Office. Evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. M.P.E.P. § 2164.05. A declaration or affidavit is, itself, evidence that must be considered. *Id.* Dr. Jevnikar's submitted declarations are supported by evidence published in peer reviewed journals that oral tolerance has been achieved in humans by Husby *et al.*, 1994 and McKown *et al.*, 2000. This evidence should not be discounted by the Office. "The examiner should **never** make the determination based on personal opinion." M.P.E.P. § 2164.05 (emphasis in original). The determination should always be based on the weight of all the evidence. *Id.*

The Examiner's remarks in the instant Official Action are primarily addressed to the Declaration of Dr. Jevnikar. Applicants provide the following response to those remarks.

With respect to the *Marketletter* (1999) reference, the Examiner has stated that Dr. Jevnikar "has not actually addressed the substance of the document, i.e. that compositions that were successful in inducing tolerance in animal models were not successful in humans."

Applicants point out that the *Marketletter* document has been addressed both in terms of its lack of credibility as a source of scientific information and as to the substance and context of the assertions therein. The *Marketletter* is a newspaper that provides business information in order that interested persons can decide whether it is a good time to buy the stock of a particular pharmaceutical company. It is not peer reviewed, nor is any of the contents of the article subject to the standards required of a scientific journal article, a patent application or an issued patent. The *Marketletter* is not an authoritative source that a practitioner of the present invention would look to for scientific information. Where, as in the present case, the question at hand is a matter of scientific results, a person of skill in the art would give the *Marketletter* little or no consideration. The *Marketletter* reference is at best, only anecdotal in nature, since this reference is not a source for reporting scientific data in an art accepted format.

As to the substance of the *Marketletter* article, it states that Autoimmune reported "substantial improvements" from baseline in each of the "core-four" parameters in phase III of the clinical trial despite the fact that the placebo effects were increased. Thus, the article contradicts the assertions of the Examiner that the compositions being tested did not have an effect in inducing tolerance. Moreover, Dr. Jevnikar pointed out that the *Marketletter* article does not state that testing of Colloral was stopped not because of it was harmful or because it had no effect, but only because the statistical significance of the results did not warrant further spending on late clinical trials. That is, the *Marketletter* is reporting a business decision, not a definitive scientific conclusion.

With respect to Goodnow (2001), Applicants respectfully submits that the Examiner is in error. The Examiner has rejected Dr. Jevnikar's explanation that the unpredictability described by Goodnow refers to the use and mechanism of action of corticosteroids. However, it is clear that the teaching of Goodnow relied upon by the Examiner to support the rejection pertains only to a conclusion regarding the action of corticosteroids. By contrast, with respect to oral tolerance it is stated on page 2118 that a phenomenon of oral tolerance exists and that clinical trials are underway involving the induction of oral tolerance. Nowhere in this section referring to oral tolerance does it say that oral tolerance does not work. Thus Goodnow, supports the general proposition that oral tolerance is achievable. Moreover, it must be noted that the Goodnow reference is not an empirical research article but a review article. Thus, the Goodnow reference includes statements of mere opinion, and in that Goodnow nether provides nor cites empirical data that convincingly refutes that oral tolerance is achievable; the Goodnow reference fails to support the allegations of the rejection.

The Examiner has also rejected Dr. Jevnikar's explanation that the WO 02/053092 ('092) publication in 2002 does not involve antigen presentation by oral administration of plant materials. The Examiner has alleged that the '092 publication teaches that "oral tolerance is fraught with numerous obstacles" and further alleges that Dr. Jevnikar failed to address the teaching of the reference that the induction of oral tolerance requires "extensive empirical experimentation" (page 23, line 15). However, this is not the focus or the objective of the disclosure of the '092 application. Rather, the '092 application only makes the cited statement with reference to other studies it describes.

In fact, the '092 publication actually demonstrates that tolerance can be accomplished and furthermore "oral and mucosal tolerance for the suppression and prevention of

inflammatory conditions is well known in the art. Examples of candidate conditions, antigens and modes of therapy, can be found..." (page 22, lines 25-27).

The Examiner has discounted the evidence presented in the references by Husby et al. (1994) and McKown et al. (2000) that were provided by Dr. Jevnikar, which demonstrate the induction of tolerance in humans. With respect to the Husby (1994) reference, it is clear that these authors demonstrated that orally fed KLH model can induce immune tolerance. The author's own conclusion is that "these studies support the concept of using Ag feeding as a treatment of certain immune-mediated diseases." This evidence cannot be disregarded. It is not appropriate to merely pick and choose from among the evidence presented in order to support a purported rejection. Therefore, the Office must accept the evidence represented by Husby and cannot merely disregard the conclusions made in Husby.

In an effort to discredit Husby, the Examiner has now cited three additional references: Moldoveanu *et al.* (2004); McKown *et al.* (1999) and a letter to the editors of *Arthritis and Rheumatism* by Carbone *et al.* (2004). However, on closer examination, these articles do not prove that the invention is not enabled as evidenced by Husby and others.

Moldoveanu (2004) does not refute the evidence of enablement represented by Husby (1994). The Examiner has alleged that both the Moldoveanu (2004) and Husby (1994) studies used the same KLH antigen model. While KLH was used as an antigen in both studies, an important point that the Examiner appears to have misapprehended is that the study protocols used in these studies were markedly different and the studies were designed with different goals in mind. Notably, the concentration of KLH used and the duration of feeding in the Moldoveanu study are different that the Husby study.

Moldoveanu (2004) study volunteers were primed systemically with 100 μg KLH followed by sustained feeding from 7-49 days and a second round of priming with 100 μg

KLH at 56 days. By contrast, in the Husby(1994) study, the volunteers were fed KLH from days 1-5 and again from 15-19 days with subcutaneous injection of 100 μg KLH at 25 and 36 days. Moldoveanu (2004) states at page 308, line 2 that "antigen feeding in experimental models of autoimmune disease is much more effective when antigen is given prior to systemic immunization rather than after." It is to be expected that the degree of immune tolerance induced by the KLH antigen may depend on the parameters specifically set forth in theses studies including dose, time and duration of exposure to the antigen.

The only thing taught by the Moldoveanu (2004) is that oral tolerance may not decrease "pre-existing" responses when this pre-existing immune response to KLH is overly robust. Studies such as Moldoveanu (2004), which seek to explore and improve the technology do not support a proposition that the presently claimed invention is not enabled. Since the Moldoveanu (2004) study did not find any changes in Th2 cytokines, this study may also teach that giving very high amounts of an antigen may abrogate the effect of oral tolerance by limiting the development of regulatory cells. Regardless, the Moldoveanu (2004) does not imply that oral tolerance as taught by Husby (1994) does not work.

The Examiner has acknowledged that the McKown *et al.* (2000) reference discloses data indicating that "oral administration of type I collagen might be useful for treating systemic sclerosis." The Examiner now cites two additional references, a letter by Carbone *et al.* (2004) and an article by McKown (1999) in which oral tolerance was not induced by administration of antigens. The Carbone letter (2004) reports that collagen I, when administered orally to patients with systemic sclerosis, was not effective at the 5 month period. Again, although the collagen I composition used was the same between Carbone (2004) and the McKown (1999), the concentration and duration of treatment is not the same between these studies. In the Carbone (2004) study, the concentration and duration of

collagen I was 10 μg/day or 100 μg/day for five months, whereas in the McKown (2000) study the concentration and duration of collagen I was 100 μg/day for one month and 500 μg/day for eleven months.

From analysis of the experimental data, the authors of the 2004 study appear to have used far lower concentrations of collagen I than was necessary to induce tolerance in the SSc patients. This is not "trial and error" as the Examiner alleges, but appears to be an attempt to determine if decreased concentrations and a shorter duration of treatment in the 2004 study would have similar outcome as the 2000 study. Such experimentation is neither undue or an indicator of the "unpredictability" of the methods. Rather, it appears to be a reasoned approach to determine the efficacy of lower concentrations of collagen I, and in so doing to improve the technology. Experiments seeking to improve a technology cannot be held to show that the technology is not enabled.

The McKown (1999) reference that was cited by the Examiner, reports a lack of efficacy of oral bovine type II collagen in the treatment of rheumatoid arthritis (RA). The authors of this study suggest possible reasons for the different outcome as compared to studies that have shown a significant improvement in RA seen with orally administered chicken collagen II (Trentham *et al.* (1993) and Barnett *et al.* (1998)). These proposed explanations include the dose and source of collagen II (i.e. bovine versus chicken), and the decision not to withdraw existing drug therapy and the protocol of the clinical trials. All of these are parameters that might be modified in routine experiments seeking to optimize a treatment protocol. What is apparent is that McKown accepts that such treatments can be effective, and is seeking to improve the technology by varying treatment parameters.

Furthermore, the Examiner has discounted the testimony of Dr. Jevnikor concerning the enablement of the invention. The inventor is one skilled in the art and with reasonable

clinical judgment and biochemical animal data available at the time soundly predicted that these results could be extrapolated to humans. Taken in view of the knowledge in the art at the time the application was filed, and the other evidence of record, it is clear that the studies described by Dr. Jevnikar in his Declaration do, in fact, demonstrate that oral tolerance can be achieved in animals and humans.

The Examiner's misapplication of the use of the term "unexpected" in Dr. Jevnikar's previous Declaration to support a basis of the rejection is an improper twisting of the inventor's meaning clearly contrary to what is true or was intended. It is inappropriate for the Examiner to remove the term "unexpected" from the context from which the term is used.

It must be recognized that in the context in which it was used, the term correctly described the fact that until the present inventors described the present invention one of skill in the art did not contemplate and would not expect that plant-derived antigens could be expressed in plants and administered orally such that the antigens are not adversely affected by digestion and thus can be more effective. The inventors of the present invention were the first to contemplate that ingestion of transgenic plants would be able to induce immune tolerance. However, given the insight, guidance and examples provided by the disclosure of the present invention, the induction of tolerance in mammals in general and humans in particular is not so unpredictable as to render the claims of the application not enabled.

The enablement requirement does not require that every variation of a method produce optimal results. Applicants have provided references describing that oral tolerance can be achieved in mammals. Applicants have demonstrated the expression of antigen in plants. Applicants have provided evidence of enablement in an art accepted animal model. Applicants demonstrated that plant material containing expressed GAD, administered orally, suppresses or reduces the immune response of a mammal to the autoantigen GAD in an

earlier filed declaration. Even if, as the Examiner asserts, there have been reports of less than optimal results under some experimental protocols, it cannot be reasonably disputed that oral tolerance has been achieved. As such, the pending claims have been demonstrated to be enabled.

In view of all the evidence submitted (including the Declarations of Dr. Jevnikar), the present application provides sufficient enablement so that one skilled in the art could make and/or use the claimed invention without undue experimentation. Thus withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 52, 59-61, 63, 69-91 and 95 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over PCT published application WO 92/07581 in view of U.S. Patent No. 5,484,719 ("the '719 patent"). The rejection is respectfully traversed.

WO 92/07581 teaches a method for suppressing an immune response by administering cell extracts from donor tissue. Nowhere in the WO 92/07581 publication is it suggested that the method administration can be oral administration of a transgenic plant.

The '719 patent does not cure the deficiencies of WO 92/07581, because the '719 patent also fails to disclose oral administration of plants for suppression of an immune response. Moreover, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). As a matter of law as stated by the Federal Circuit, one skilled in the art would not be motivated to combine these two references, because doing so would change the principle of operation of the '719 patent and because the objectives of the two references are diametrically opposed.

The objective of the '719 patent is the opposite of the objective of the present application. The '719 patent teaches that expression of antigens from viral, bacterial or fungal antigens in a plant for a method of oral vaccination will have the effect of increasing the immune response. The present application is directed to the induction of oral tolerance with tolerogenic antigens with the object of suppressing an immune response. The Examiner refers to induction of an immune response and induction of immune tolerance as "two side of the same coin." But that is to say they are opposites, the two objectives have opposing goals and opposing principles.

If oral ingestion were to induce tolerance to the viral, bacterial or fungal antigens of the '719 patent, it would be the opposite of the desired effect. The Federal Circuit has held that if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). The predecessor of the Federal Circuit held that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (CCPA 1959).

Thus, the combination of references fails to teach every element of the claimed invention. Moreover, as a matter of law, there would have been no motivation to combine the cited references. For at least these reasons, the proposed combination fails to support a *prima facie* case of obviousness. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

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